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(54) Title: 4,5-DIHYDRO-1H-PYRAZOLE DERIVATIVES HAVING CB1-ANTAGONISTIC ACTIVITY

(57) Abstract: The present invention relates to a group of novel 4,5-dihydro-1H-pyrazole derivatives having S configuration at the 4-position of their 4,5-dihydro pyrazole ring which are potent antagonists of the cannabis CB_1-receptor.The compounds have the general formula (I) wherein- R and R_1 are the same or different and represent 3-pyridyl or 4-pyridyl or phenyl which may be substituted with halogen or methoxy,- R_2 and R_3 are the same or different and represent hydrogen, alkyl (1-3 C) or dimethylamino- R_4 represents phenyl which may be substituted with 1 or 2 substituents selected from the group halogen atoms, trifluoromethyl, methoxy and alkyl (1-3 C)and tautomers, prodrugs and salts thereof.These enantiomers are much more potent and selective antagonists of the cannabis CB_1-receptor, than the other enantiomer.

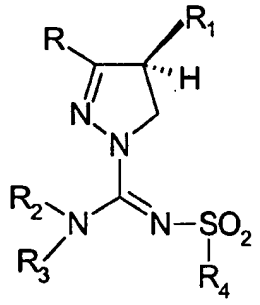
4,5-Dihydro-1H-pyrazole derivatives having CB_1-antagonistic activity

The present invention relates to a group of novel enantiomers of 4,5-dihydro-1H-pyrazole derivatives having S configuration at the 4-position of their 4,5-dihydropyrazole ring, to methods for the preparation of these compounds, and to pharmaceutical compositions containing one or more of these compounds as an active component.
The above mentioned (4S)-4,5-dihydro-1H-pyrazoles are potent Cannabis-1 (CB_1) receptor antagonists with utility for the treatment of psychiatric and neurological disorders.

Cannabinoids are present in the Indian hemp *Cannabis Sativa L.* and have been used as medicinal agents for centuries (Mechoulam, R.; Feigenbaum, J.J. *Prog. Med. Chem.* **1987**, *24*, 159). However, only within the past ten years the research in the cannabinoid area has revealed pivotal information on cannabinoid receptors and their (endogenous) agonists and antagonists. The discovery and the subsequent cloning of two different subtypes of Cannabinoid receptors (CB_1 and CB_2) stimulated the search for novel cannabinoid receptor antagonists (Munro, S.; Thomas, K.L.; Abu-Shaar, M. *Nature* **1993**, *365*, 61. Matsuda, L.A.; Bonner, T.I. *Cannabinoid Receptors*, Pertwee, R.G. Ed. **1995**, 117, Academic Press, London). In addition, pharmaceutical companies became interested in the development of cannabinoid drugs for the treatment of diseases connected with disorders of the cannabinoid system. The wide distribution of CB_1 receptors in the brain, in combination with the strictly peripheral localisation of the CB_2 receptor, makes the CB_1 receptor a very interesting molecular target for CNS-directed drug discovery in the areas of both psychiatric and neurological disorders (Consroe, P. *Neurobiology of Disease* **1998**, *5*, 534. Pop, E. *Curr. Opin. In CPNS Investigational Drugs* **1999**, *1*, 587. Greenberg, D.A. *Drug News Perspect.* **1999**, *12*, 458). Hitherto, three types of distinct CB_1 receptor antagonists are known. Sanofi disclosed their diarylpyrazole congeners as selective CB_1 receptor antagonists. A representative example is SR-141716A, which is currently undergoing Phase II clinical development for psychotic disorders (Dutta, A.K.; Sard, H.; Ryan, W.; Razdan, R.K.; Compton, D.R.; Martin, B.R. *Med. Chem. Res.* **1994**, *5*, 54. Lan, R.; Liu, Q.; Fan, P.; Lin, S.; Fernando, S.R.; McCallion, D.; Pertwee, R.; Makriyannis, A. *J. Med. Chem.* **1999**, *42*, 769. Nakamura-Palacios, E.M.; Moerschbaecher, J.M.; Barker, L.A. *CNS Drug Rev.* **1999**, *5*, 43). Aminoalkylindoles have been disclosed as CB_1 receptor antagonists. A representative example is Iodopravadoline (AM-630), which was introduced in

1995. AM-630 is a CB_1 receptor antagonist, but sometimes behaves as a weak partial agonist (Hosohata, K.; Quock, R.M.; Hosohata, Y.; Burkey, T.H.; Makriyannis, A.; Consroe, P.; Roeske, W.R.; Yamamura, H.I. *Life Sc.* **1997**, *61*, PL115). More recently, researchers from Eli Lilly described aryl-aroyl substituted benzofurans as selective CB_1 receptor antagonists (*e.g.* LY-320135) (Felder, C.C.; Joyce, K.E.; Briley, E.J.; Glass, M.; Mackie, K.P.; Fahey, K.J.; Cullinan, G.J.; Hunden, D.C.; Johnson, D.W.; Chaney, M.O.; Koppel, G.A.; Brownstein, M. *J. Pharmacol. Exp. Ther.* **1998**, *284*, 291). Recently, 3-alkyl-5,5'-diphenylimidazolidinediones were described as cannabinoid receptor ligands, which were indicated to be cannabinoid antagonists (Kanyonyo, M.; Govaerts, S.J.; Hermans, E.; Poupaert, J.H., Lambert, D.M. *Biorg. Med.Chem. Lett.* **1999**, *9*, 2233). Interestingly, many CB_1 receptor antagonists have been reported to behave as inverse agonists *in vitro* (Landsman, R.S.; Burkey, T.H.; Consroe, P.; Roeske, W.R.; Yamamura, H.I. *Eur. J. Pharmacol.* **1997**, *334*, R1). Recent reviews provide a nice overview of the current status in the cannabinoid research area (Mechoulam, R.; Hanus, L.; Fride, E. *Prog. Med. Chem.* **1998**, *35*, 199. Lambert, D.M. *Curr. Med. Chem.* **1999**, *6*, 635. Mechoulam, R.; Fride, E.; Di Marzo, V. *Eur. J. Pharmacol.* **1998**, *359*, 1).

It has now surprisingly been found that the novel enantiomers of 4,5-dihydro-1H-pyrazole derivatives having S configuration at the 4-position of their 4,5-dihydro pyrazole ring of the formula (I), prodrugs thereof, tautomers thereof and salts thereof



(I)

wherein

- R and R_1 are the same or different and represent 3-pyridyl or 4-pyridyl, or phenyl which may be substituted with halogen or methoxy,
- R_2 and R_3 are the same or different and represent hydrogen, alkyl (1-3 C) or dimethylamino
- R_4 represents phenyl which may be substituted with 1, 2 or 3 substituents selected from the group halogen, trifluoromethyl, methoxy and alkyl (1-3 C)

are much more potent and selective antagonists of the cannabis CB_1-receptor, than the correspondence R-enantiomer.

Due to the potent CB_1 antagonistic activity the compounds according to the invention are suitable for use in the treatment of psychiatric disorders such as psychosis, anxiety, depression, attention deficits, memory disorders and appetite disorders, obesity, neurological disorders such as dementia, distonia, Parkinson's disease, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, cerebral ischaemia, as well as for the treatment of pain disorders and other CNS-diseases involving cannabinoid neurotransmission, and in the treatment of gastrointestinal disorders and cardiovascular disorders.

The affinity of the compounds of the invention for cannabinoid CB_1 receptors was determined using membrane preparations of Chinese hamster ovary (CHO) cells in which the human cannabis CB_1 receptor is stably transfected in conjunction with [3H]CP-55,940 as radioligand. After incubation of a freshly prepared cell membrane preparation with the [3H]-ligand, with or without addition of compounds of the invention, separation of bound and free ligand was performed by filtration over glassfiber filters. Radioactivity on the filter was measured by liquid scintillation counting.

The cannabinoid CB_1 antagonistic activity of compounds of the invention was determined by functional studies using CHO cells in which human cannabinoid CB_1 receptors are stably expressed. Adenylyl cyclase was stimulated using forskolin and measured by quantifying the amount of accumulated cyclic AMP. Concomitant activation of CB_1 receptors by CB_1 receptor agonists (*e.g.* CP-55,940 or (R)-WIN-55,212-2) can attenuate the forskolin-induced accumulation of cAMP in a concentration-dependent manner. This CB_1 receptor-mediated response can be antagonised by CB_1 receptor antagonists such as the compounds of the invention.

The invention relates both to the E isomer, Z isomer and E/Z mixtures of compounds having formula (I).

The compounds can be brought into forms suitable for administration by means of usual processes using auxiliary substances and/or liquid or solid carrier materials.

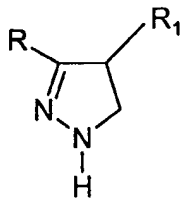
The compounds of the invention having formula (III) (*vide infra*) can be obtained according to methods known, for example: a) EP 0021506; b) DE 2529689.

A suitable synthesis for the racemic compounds according to the present invention is the following:

Synthesis route A

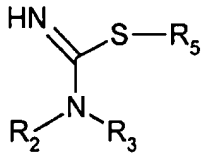
Step 1 of route A

Reaction of a compound having formula (III)



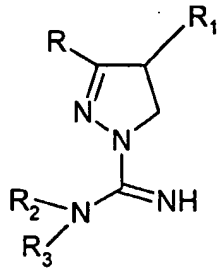
(III)

with a compound having formula (IV)



(IV)

wherein R_5 represents a lower alkyl group, such as for example 2-methyl-2-thiopseudourea, or with a suitable salt form thereof in the presence of a base. This reaction gives a 4,5-dihydro-1H-pyrazole-1-carboxamidine derivative having formula (V)



(V)

wherein the symbols have the meanings as mentioned above. Compounds having formula (V) wherein R, R_1, R_2 and R_3 have the meaning as described herein above for compound (I) are new.

Alternatively, a compound having formula (III) is reacted with a so-called guanylating agent. Examples of such guanylating agents are 1H-pyrazole-1-carboxamidine and its salts (for example the hydrochloride salt) and 3,5-dimethyl-1H-pyrazole-1-carboxamidine and its salts (for example the nitrate salt) and the like. This reaction gives a carboxamidine derivative having formula (V).

Alternatively, a compound having formula (III) is reacted with a so-called protected guanylating agent. Examples of such protected guanylating agents are N-(benzyloxycarbonyl)-1H-pyrazole-1-carboxamidine, N-(*tert*-butoxycarbonyl)-1H-pyrazole-1-carboxamidine and N,N'-bis-(*tert*-butoxycarbonyl)-1H-pyrazole-1-carboxamidine and the like. This reaction gives after deprotection a compound having formula (V).

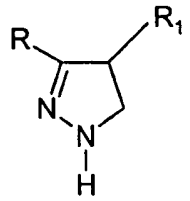
Step 2 of route A

The compound having formula (V) is reacted with an optionally substituted compound of the formula R_4-SO_2X, wherein R_4 has the above mentioned meaning and X represents a halogen atom. This reaction is preferably carried out in the presence of a base, such as triethylamine in an aprotic solvent, such as acetonitrile.

Synthesis route A1

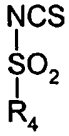
Step 1 of route A1

Reaction of a compound having formula (III)



(III)

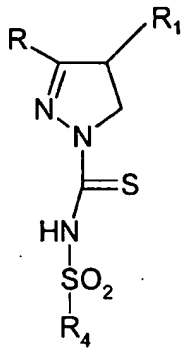
with a thioisocyanate derivative having formula (VI) .



(VI)

This reaction is preferably carried out in an inert organic solvent, such as for example acetonitrile.

This reaction gives a thiocarboxamide derivative having formula (VII). Compounds having formula (VII) wherein R, R_1 and R_4 have the meaning as described herein above for compound (I) are new.



(VII)

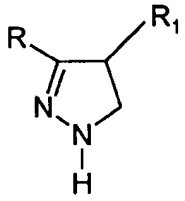
Step 2 of route A1

Reaction of a compound having formula (VII) with an amine in the presence of a mercury(II) salt, such as for example $HgCl_2$, gives a compound having formula (I) This reaction is preferably carried out in a polar organic solvent, such as for example acetonitrile.

Synthesis route A2

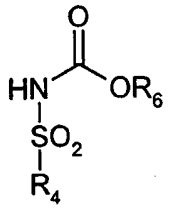
Step 1 of route A2

Reaction of a compound having formula III



(III)

with a carbamate ester derivative having formula (VIII).

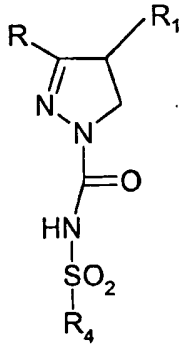


(VIII)

wherein R_6 represents a lower alkyl group, for example methyl.

This reaction is preferably carried out in an inert organic solvent, such as for example 1,4-dioxane.

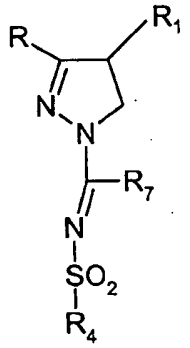
This reaction gives a 4,5-dihydropyrazole-1-carboxamide derivative having formula (IX). Compounds having formula (IX) wherein R, R_1 and R_4 have the meaning as described herein above for compound (I) are new.



(IX)

Step 2 of route A2

Reaction of a compound having formula (IX) with a halogenating agent, such as for example PCl_5, gives a 4,5-dihydropyrazole-1-carboximidoyl halogenide derivative having formula (X) .



(X)

wherein R_7 represents a halogen atom, such as for example chloro. This reaction is preferably carried out in an inert organic solvent, such as for example chlorobenzene.

Compounds having formula (X) wherein R, R_1 and R_4 have the meaning as described herein above for compound (I) and wherein R_7 represents a halogen atom are new.

Step 3 of route A2

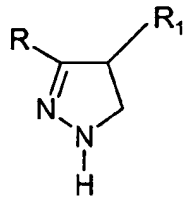
Reaction of a compound having formula (X) with an amine gives a compound having formula (I).

This reaction is preferably carried out in an inert organic solvent, such as for example dichloromethane.

Synthesis route A3

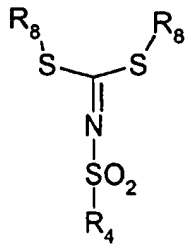
Step 1 of route A3

Reaction of a compound having formula III



(III)

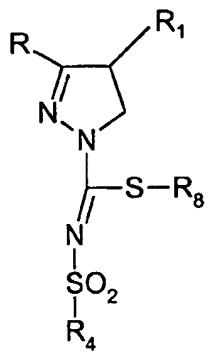
with a dithioimidocarbonic ester derivative having formula (XI) .



(XI)

wherein R_8 represents a C_{1-3} alkyl group.

This reaction is preferably carried out in a polar organic solvent, such as for example acetonitrile.



(XII)

This reaction gives a carboximidothioic ester derivative having fomula (XII).

Compounds having formula (XII) wherein R, R_1 and R_4 have the meaning as described herein above for compound (I) and wherein R_8 represents a C_{1-3} alkyl group are new.

Step 2 of route A3

Reaction of a compound having formula (XII) with an amine gives a compound having formula (I).

This reaction is preferably carried out in a polar organic solvent, such as for example methanol.

Example I

3-(4-Chlorophenyl)-4,5-dihydro-N-((4-fluorophenyl)sulfonyl)-4-phenyl-1H-pyrazole-1-carboxamidine

Part A: A stirred mixture of 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (5.13 gram, 20.0 mmol), 2-methyl-2-thiopseudourea hydroiodide (5.00 gram, 23.0 mmol) and pyridine (10 ml) is heated at 110 °C for 1 hour. After one night standing at room temperature diethyl ether is added and the precipitate is collected by filtration. This precipitate is washed three times with diethyl ether portions to afford a solid (9 gram). Melting point: ~230 °C. This solid is dissolved in methanol (20 ml). To the resulting solution is successively added a 2N sodium hydroxide solution (12 ml) and water (200 ml). The formed precipitate is collected by filtration, washed two times with diethyl ether and successively with diisopropyl ether. The resulting solid is dried *in vacuo* to yield 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine (5.1 gram, 88 % yield). Melting point: 187-189 °C.

Part B: To a stirred mixture of 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine (0.50 gram, 1.68 mmol) and 4-fluorophenylsulfonyl

chloride (0.34 gram, 1.75 mmol) in acetonitrile (10 ml) is added N,N-dimethyl-4-aminopyridine (0.020 gram, 0.175 mmol) and triethylamine (1 ml). The resulting solution is stirred at room temperature for 30 minutes. After addition of a 2N sodium hydroxide solution and extraction with ethylacetate (400 ml), the ethylacetate layer is concentrated *in vacuo*. The resulting crude residue is further purified by means of flash chromatography (petroleum ether/diethyl ether = 1/1 (v/v), followed by ethylacetate). Subsequent concentration *in vacuo* affords solid 3-(4-chlorophenyl)-4,5-dihydro-N-((4-fluorophenyl)sulfonyl)-4-phenyl-1H-pyrazole-1-carboxamidine (0.55 gram, 72 % yield). Melting point: 214-215 °C

In an analogous manner the compounds having formula (I) listed below have been prepared:

4,5-Dihydro-N-((4-fluorophenyl)sulfonyl)-3-(4-methoxyphenyl)-4-(4-methoxyphenyl)-1H-pyrazole-1-carboxamidine: Melting point: 155-156 °C

4,5-Dihydro-3-(4-methoxyphenyl)-4-(4-methoxyphenyl)-N-((4-methoxyphenyl)sulfonyl)-1H-pyrazole-1-carboxamidine: Melting point: 148-150 °C

3-(4-Chlorophenyl)-4,5-dihydro-4-phenyl-N-((2,4,6-trimethylphenyl)sulfonyl)-1H-pyrazole-1-carboxamidine: Melting point: 221-222 °C

Example II

N^1,N^1-Dimethyl-N^2-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine

Part A: A stirred mixture of 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (12.0 gram, 46.8 mmol), [(4-chlorophenyl)sulfonyl]dithioimidocarbonic acid dimethyl ester (CAS: 13068-12-7) (9.20 gram, 31.1 mmol) and triethylamine (15 ml) in acetonitrile (200 ml) is heated at reflux temperature for 20 hours. An additional portion of 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (12.0 gram, 46.8 mmol) is added and the resulting mixture is heated at reflux temperature for another 16 hours. After concentration *in vacuo,* dichloromethane is added and the resulting solution is washed twice with water and dried over anhydrous Na_2SO_4. After filtration and evaporation *in vacuo* the residue is further purified by flash chromatography (diethyl ether/ petroleum ether = 1/1 (v/v)) to give 3-(4-chlorophenyl)-N-((4-chlorophenyl)sulfonyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboximidothioic acid methyl ester (12.5 gram, 80% yield based on [(4-chlorophenyl)sulfonyl]dithioimidocarbonic acid dimethyl ester) as an amorphous solid.

Part B: To a stirred mixture of 3-(4-chlorophenyl)-N-((4-chlorophenyl)sulfonyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboximidothioic acid methyl ester (4.20 gram, 8.30 mmol) in methanol (75 ml) is added dimethylamine (10 ml) and dichloromethane (75 ml) and the resulting solution is stirred at room temperature for 6 hours. Evaporation *in vacuo* and subsequent flash chromatographic purification (diethyl ether/ petroleum ether = 1/1 (v/v), followed by diethyl ether) gives a solid which is further purified by recrystallisation from diisopropyl ether to yield N^1-dimethyl-N^2-((4-chloro-phenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine (2.63 gram, 63 % yield). Melting point: 182 °C.

In an analogous manner the compounds having formula (I) listed below have been prepared:
N-Methyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-(3-pyridyl)-1H-pyrazole-1-carboxamidine. Melting point: 101-105 °C.
N-Methyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-(4-pyridyl)-1H-pyrazole-1-carboxamidine. Melting point: 112-115 °C.

Example III

N-Methyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine

Part A: To a solution of N-((4-chlorophenyl)sulfonyl)carbamic acid methyl ester (CAS: 34543-04-9) (2.99 gram, 12.0 mmol) and pyridine (4 ml) in 1,4-dioxane (20 ml) is added 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (3.39 gram, 13.2 mmol) and the resulting mixture is stirred for 4 hours at 100 °C. After concentration *in vacuo* the residue is dissolved in dichloromethane, successively washed with water, 1N HCl and water, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to a volume of 20 ml. Methyl-tert-butyl ether (60 ml) is added and the resulting solution is concentrated to a volume of 20 ml. The formed crystals are collected by filtration and recrystallised from methyl-*tert*-butyl ether to give 3-(4-chlorophenyl)-N-((4-chlorophenyl)sulfonyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide (4.75 gram, 76 % yield) Melting point: 211-214 °C.

Part B: A mixture of 3-(4-chlorophenyl)-N-((4-chlorophenyl)sulfonyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide (3.67 gram, 7.75 mmol) and phosphorus pentachloride (1.69 gram, 8.14 mmol) in chlorobenzene (40 ml) is heated at reflux for 1 hour. After thorough concentration *in vacuo*, the formed N-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-

carboximidoyl chloride is suspended in dichloromethane and reacted with cold methylamine (1.5 ml). After stirring at room temperature for 1 hour, the mixture is concentrated *in vacuo*. The residue is crystallised from diethyl ether to give N-methyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine (2.29 gram, 61 % yield). Melting point: 96-98 °C (dec.).

In an analogous manner the compounds having formula (I) listed below have been prepared:

N-Methyl-N'-((3-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl - 1H-pyrazole-1-carboxamidine. Melting point: 156-160 °C.

N-Propyl-N'-((4-fluorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 129-138 °C.

N-(2-Propyl)-N'-((4-fluorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 110-112 °C.

N-(2-Propyl)-N'-((4-chlorophenyl)sulfonyl)-3-(4-pyridyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: Amorphous.

N^1-Ethyl-N^1-methyl-N^2-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 184 °C.

N^1-Ethyl-N^1-methyl-N^2-((4-fluorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 173-176 °C.

N^1,N^1-Dimethyl-N^2-((4-(trifluoromethyl)phenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 195-196 °C.

N^1,N^1-Dimethyl-N^2-((3-methylphenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 195-198 °C.

N^1,N^1-Dimethyl-N^2-((3-methoxyphenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 204-206 °C.

N-Ethyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: Amorphous.

N-Dimethylamino-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 155-159 °C.

N-Methyl-N'-((4-(trifluoromethyl)phenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: Amorphous.

N^1,N^1-Dimethyl-N^2-((2-methylphenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point:148-151 °C.

N-Methyl-N'-((2,4-difluorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 85 °C.

Example IV

(-)-(4S)-N-methyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine

(-)-(4S)-N-Methyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine (7.16 gram, 0.0147 mol)) ($[\alpha^{25}_D]$ = -150°, c = 0.01, MeOH) (melting point: 169-170 °C) was obtained via chiral chromatographic separation of racemic N-methyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine (18 gram, 0.037 mol) using a Chiralpak AD, 20 µm chiral stationary phase. The mobile phase consisted of a mixture of hexane/ethanol (80/20 (v/v)) and 0.1 % ammonium hydroxide (25 % aqueous solution).

In an analogous manner the optically pure compounds listed below have been prepared from the corresponding racemates:

(-)-(4S)-N-Ethyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine: ($[\alpha^{25}_D]$ = -126 °, c = 0.01, $CHCl_3$); Melting point: 172-175 °C. Stationary phase: Chiralcel OD. Mobile phase: A mixture of heptane/2-propanol (85/15 (v/v)).

(-)-(4S)-N-Dimethylamino-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine: ($[\alpha^{25}_D]$ = -132 °, c = 0.01, $CHCl_3$); Melting point: 218-224 °C. Stationary phase: Chiralcel OD. Mobile phase: A mixture of heptane/2-propanol (85/15 (v/v)).

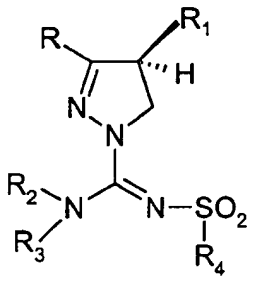
(-)-(4S)-N-Methyl-N'-((4-(trifluoromethyl)phenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine: ($[\alpha^{25}_D]$ = -131 °, c = 0.01, $CHCl_3$); Melting point: 157-160 °C. Stationary phase: Chiralcel OD. Mobile phase: A mixture of heptane/2-propanol (85/15 (v/v)).

(-)-(4S)-N^1,N^1-Dimethyl-N^2-((2-methylphenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine: ($[\alpha^{25}_D]$ = -88 °, c = 0.01, MeOH); Melting point: Amorphous. Stationary phase: Chiralpak AD. Mobile phase: Ethanol.

(-)-(4S)-N-Methyl-N'-((2,4-difluorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine: ($[\alpha^{25}_D]$ = -129 °, c = 0.01, MeOH); Melting point: Amorphous. Chiralpak AD. Mobile phase: Methanol.

Claims

1. The enantiomer having S configuration at the 4-position of their 4,5-dihydro pyrazole ring of a compound of formula (I)



(I)

wherein

- R and R_1 are the same or different and represent 3-pyridyl or 4-pyridyl, or phenyl which may be substituted with halogen or methoxy,
- R_2 and R_3 are the same or different and represent hydrogen, alkyl (1-3 C) or dimethylamino
- R_4 represents phenyl which may be substituted with 1, 2 or 3 substituents selected from the group halogen atoms, trifluoromethyl, methoxy and alkyl (1-3 C)

and tautomers, prodrugs and salts thereof.

2. A compound having formula (I) as claimed in claim 1, wherein R is the group 4-chlorophenyl, R_1 is phenyl, R_2 is hydrogen, R_3 is methyl and R_4 represents 4-chlorophenyl, and salts thereof.

3. A pharmaceutical composition containing at least one compound as claimed in claim 1 as an active component.

4. A method of preparing pharmaceutical compositions characterized in that a compound as claimed in claim 1 is brought in a form suitable for administration.

5. Process for the preparation of compounds having formula I, characterized in that the racemic mixture of a compound having formula I is separated into the levorotatory and the dextrorotatory enantiomers.

6. A method of treating psychiatric disorders such as psychosis, anxiety, depression, attention deficits, memory disorders and appetite disorders, obesity, neurological disorders such as Parkinson's disease, dementia, distonia, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, ischaemia, pain and other CNS-diseases involving cannabinoid neurotransmission, characterized in that a compound as claimed in claim 1 is used.

7. A method of treating gastrointestinal disorders involving cannabinoid neurotransmission, characterized in that a compound as claimed in claim 1 is used.

8. A method of treating cardiovascular disorders involving cannabinoid neurotransmission, characterized in that a compound as claimed in claim 1 is used.

INTERNATIONAL SEARCH REPORT

Interr ial Application No
PCT/EP 02/03079

A. CLASSIFICATION OF SUBJECT MATTER
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

Inter ial Application No
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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

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(74) Agents: **VOLPE, Anthony, S.** et al.; Volpe and Koenig, P.C., Suite 400, One Penn Center, 1617 John F. Kennedy Boulevard, Philadelphia, PA 19103 (US).

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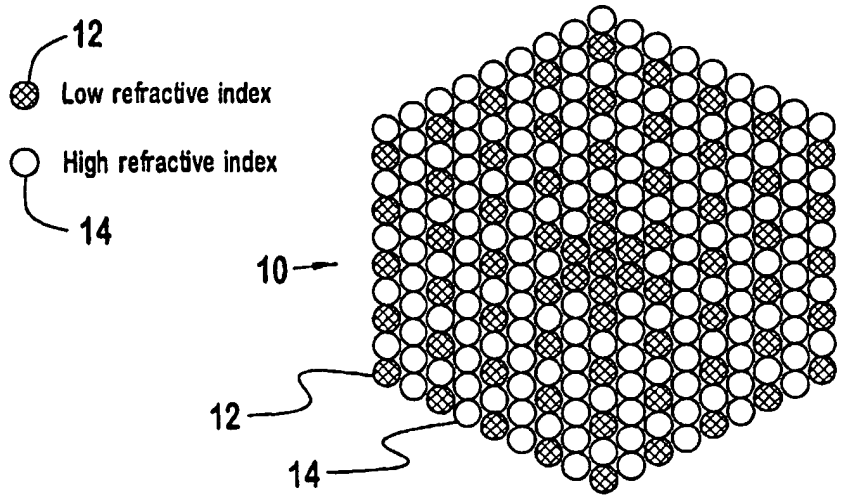
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: MULTI-COMPONENT ALL GLASS PHOTONIC BAND-GAP FIBER



(57) Abstract: Low refractive index glass rods (12) and high refractive index glass rods (14) are assembled in a pattern to create a preform (10). This preform is then heated and drawn to form the non-porous photonic band-gap fiber.

WO 02/26648 A1

MULTI-COMPONENT ALL GLASS PHOTONIC BAND-GAP FIBER

BACKGROUND

The present invention relates to a photonic crystal fiber, and more particularly, to a novel method of fabricating a photonic crystal fiber, having a non-porous, all glass structure.

Communication systems which utilize optical fibers are known. These fibers typically achieve guiding of light by means of total internal reflection, based on the presence of a solid core of a relatively high refractive index that is surrounded by a solid cladding that has a relatively low refractive index.

A new type of optical fiber has recently been proposed which is referred to as a "photonic crystal" or "photonic band gap" (PBG) fiber. The PBG fibers involve a structure having a refractive index that varies periodically in space (in the X-Y plane). This type of optical fiber is discussed in several articles including J.C. Knight et al., *Optics Letters*, Vol. 21, No. 19, P. 15-47 (October 1996); T.A. Burkes, et al., *Optics Letters*, Vol. 22, No. 13, P. 961 (July 1997). These PBG fibers are typically fabricated with silica fiber having air gaps in order to achieve a periodic structure in the array which has a large index difference. This is achieved by the air gaps in combination with the silica fiber creating a lower refractive index in comparison to the areas having silica fiber alone. The air gaps are typically created by a multiple stack and draw process in which the air gaps are formed by holes drilled in silica rod preforms which are then stacked and drawn in order to create the PBG fiber structure.

A PBG fiber is also known in which that it was discovered that there was no need for a periodicty in the X-Y plane (cross-section) of the fiber. It was found that if the fiber possesses a core region having a refractive index that is significantly higher than the effective index of a fraction of a cladding region that surrounds the core region which comprises the multiplicity of micro structural cladding features such as capillary voids, that a periodic array was not necessarily required. However, capillary voids are still

utilized as the primary means of forming the cladding material. However, the voids may be filled with metal or glass with a lower melting temperature than the capillary tube material in a subsequent operation with a second melt at a lower temperature. This introduces additional manufacturing time and costs, and also raises additional quality control issues.

The prior art process of making PBG fibers is difficult and costly, and it would be desirable to have simpler, less costly methods for making PBG fibers. Furthermore, these porous fibers are problematic for use in systems where it is necessary to have a solid or vacuum tight connection. It is also difficult to achieve a small bend radius with porous PBG fibers without damaging the fibers.

SUMMARY

Briefly stated, the present invention provides a method of producing an all glass, non-porous, multi-component photonic band-gap fiber which includes the steps of creating a preform having a plurality of low refractive index glass rods and a plurality of high refractive index glass rods arranged in a pre-determined pattern between the low refractive index glass rods. The preform is heated and drawn to form a non-porous photonic band-gap fiber.

In another aspect, the invention provides for the assembly of the preform from a plurality of preform subassemblies which each have a predetermined number of low refractive index and high refractive index glass rods arranged in a predetermined pattern.

In another aspect, a method producing an all glass, non-porous, multi-component photonic band-gap multiple array is provided. The method includes creating a first PBG fiber by assembling a first preform having a plurality of low refractive index glass rods and a plurality of high refractive index glass rods which are arranged in a predetermined pattern between the low refractive index glass rods. The first preform is heated and drawn to form a first drawn non-porous subassembly having a first index. A second PBG fiber is created by assembling a second preform having a plurality of low refractive index glass rods and a plurality of medium refractive index glass rods which are arranged in a predetermined pattern between the low index glass rods. The second preform is heated

and drawn to form a second drawn non-porous subassembly having a second index. A third preform is assembled from the first and second drawn non-porous subassemblies

The third preform is heated and drawn to form a non-porous multi-component PBG multiple index array.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a cross-sectional view of a PBG fiber in accordance with the present invention;

Figure 2 is a cross-sectional view of a second embodiment of a PBG fiber in accordance with the present invention;

Figure 3 is a cross-sectional view of a third preferred embodiment of a PBG fiber in accordance with the present invention;

Figure 4 is a cross-sectional view of a PBG array in accordance with the present invention;

Figure 5 is a cross-sectional view of a PBG preform subassembly in accordance with the present invention;

Figure 6 is a cross-sectional view of a fourth embodiment of a PBG fiber formed from the assembly of the PBG subassembly shown in Figure 5;

Figure 7 is a cross-sectional view of a PBG array having multiple indexes in accordance with the present invention;

Figure 8 is a cross-sectional view of a sixth embodiment of a PBG fiber formed from multiple index materials;

Figure 9 is a cross-sectional view of a PBG fiber having a Gain Medium located in the fiber; and

Figure 10 is a schematic view of an optical fiber communication system comprising a PBG fiber in accordance with the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Referring now to Figure 1, a photonic band-gap ("PBG") fiber 10 is shown in cross-section in the X-Y plane. This plane is normal to the longitudinal (Z) direction of the fiber, which can extend a substantial distance for transmission of an optic signal. The first embodiment of the PBG fiber 10 is formed from a first plurality of low refractive index glass rods 12 and a plurality of high refractive index glass rods 14 arranged in a predetermined pattern between the low refractive index glass rods 12. The specific arrangement of the high index and low index glass rods 14, 12 in the preform will determine the specific band-gaps in the light that can be transmitted through the fiber 10. The preform is then heated and drawn in the manner well known to those skilled in the art to form a non-porous photonic band-gap fiber 10 having a diameter of approximately 125 microns. During the drawing process, the individual glass rods in the PBG fiber 10 are drawn down to a size of approximately 0.25 microns. Preferably, the low refractive index glass rods have an index on the order of 1.47 and the high refractive index glass rods have an index over 1.81. However, different low and high refractive indices can be used depending upon the specific properties required. During the drawing process, the rods are fused together to form a solid, non-porous structure in cross-section which allows the finished PBG fiber 10 to be vacuum tight. The solid PBG fiber offers better mechanical structure and stability than the prior known PBG fibers which utilize capillary air gaps as defects in order to form the PBG fibers.

While the first preferred embodiment of the fiber 1 is shown as being hexagonal in cross-section, other cross-sectional shapes, such as squares, circles or other forms can be utilized if desired. Additionally different arrangements of the low and high index glass rods 12, 14 can be utilized.

Referring now to Figure 2, a second preferred embodiment of a PBG fiber 20 is shown. In the second preferred embodiment, a periodic structure is achieved in the array by arranging the low index and high index glass rods 12 and 14 in concentric rings in the preform. In the second preferred embodiment, a low refractive index glass rod 12 is located in the center of the preform. The preform is heated and drawn in order to form the PBG fiber 20.

Referring now to Figure 3, a third preferred embodiment of a PBG fiber 30 is shown. In this case, the low refractive index glass rods 12 are dispersed in a pattern such that each low refractive glass rod 12 is surrounded by six high index glass rods 14.

Referring now to Figure 4, a PBG array in accordance with a fourth preferred embodiment of the invention is shown. The PBG array 40 is formed by assembling a first stage preform subassembly having a predetermined number of the low refractive index glass rods 12 and the high refractive index glass rods 14 arranged in a predetermined pattern, such as the pattern shown in Figure 1 for the PBG fiber 10. The glass rods in the first stage preform subassembly are heated and drawn to form drawn first-stage subassemblies. A second preform is created from a plurality of the drawn first stage subassemblies. This second preform is then heated and drawn to a desired size and can be used to make a face plate array of a larger size, such as 3 inch diameter plates, or can be drawn down to a smaller size, such as 125 microns in order to form a PBG fiber.

Referring now to Figures 5 and 6, smaller preform subassembly 50 can be created from the low index glass rods 12 and high index glass rods 14. The smaller preform subassemblies 50 are drawn to form drawn preform assemblies which can then be utilized to create a preform for a PBG fiber 51 in accordance with a fifth preferred embodiment of the present invention. Again, during the drawing process, all air is removed from the fiber to form a solid glass PBG fiber.

Referring now to Figure 7, a portion of a PBG array 16 in accordance with a sixth preferred embodiment of the invention is shown. The PBG array is assembled utilizing drawn preforms similar to that discussed above in connection with Figure 1. A first photonic band-gap optical fiber preform is assembled having a plurality of low refractive index glass rods 12 and a plurality of high refractive index glass rods 14 arranged in a pre-determined pattern between the low refractive index glass rods 12. The preform is heated and drawn to form a first drawn non-porous subassembly having a first index. A second photonic band-gap optical fiber 11 is assembled as a second preform having a plurality of low refractive index glass rods 12 and a plurality of medium refractive index glass rods 16 arranged in a predetermined pattern, which is shown as being the same as

the pattern utilized to create the first PBG fiber 10. The second preform is heated and drawn to form the second drawn non-porous subassembly 11 having a second index. A third preform is assembled from a plurality of the first and second drawn non-porous subassemblies 10 and 11. The third preform is then heated and drawn to form a non-porous multi-photonic band-gap multiple index array 60. The number of subassemblies 10 and 11 utilized in the array can be varied depending upon the particular application. Additionally, the shape of the first and second drawn non-porous subassemblies can be varied depending upon the particular application. Preferably, the medium refractive index glass rods 16 have an index of 1.6. However, those skilled in the art will recognize that other different indices can be utilized depending upon the effect desired.

Referring now Figure 8, a seventh preferred embodiment of a PBG fiber 70 is shown. The PBG fiber 70 is assembled from low, medium and high refractive index glass rods 12, 14 and 16 which are assembled in a preform in a desired pattern. The preform is heated and drawn in order to form the PBG fiber 70. This has the advantage of allowing for control of fiber dispersion properties.

Referring now to Figure 9, and eighth preferred embodiment of a PBG fiber 80 is shown. The PBG fiber 80 is comprised of a plurality of low index and high index glass rods 12 and 14 which are arranged in a preform. A gain medium 18, which preferably comprises doped glass rods, is located in the center of the preform. The preform is heated and drawn in order to form the eighth preferred embodiment of the PBG fiber 80.

The use of a gain medium in this arrangement has particular advantage for use in forming an amplifier or a laser if appropriate reflective and coupling coatings are provided on the ends of a segment of the PBG fiber 80 thus formed, in order to intensify light energy which enters the gain medium, or provide lasing.

The above-noted embodiments of the PBG fiber and/or arrays are intended to be examplary only, and different glass layouts and fibers counts can be employed. All of the embodiments of the PBG fiber offer lower cost manufacture and improved mechanical structural stability in comparison to the known prior art PBG fibers which

utilize capillary air openings as the defect in the fibers. This allows tight bend angles which were not possible with the prior known PBG fibers, and forming the present PBG fiber as a solid, vacuum tight material, allows for use in different applications. A particularly advantageous application is for use in fiber optic communication systems, where the PBG fiber is located between a light signal transmitter 92 and a light signal receiver 94, as shown in Figure 10.

Another useful property provided by the PBG drawn fiber is that it provides a useful means for locating defects in the final product. It has been observed experimentally that light inserted in the PBG can not propogate in the ordered regions (as expected), but can find the defects, such as missing or misplaced fibers, and be guided therein. This allows the defects in an array of drawn fibers to be measured.

While the preferred embodiments of the invention have been described in detail, the invention is not limited to the specific embodiments described above, which should be considered as merely exemplary. Further modifications and extensions of the present invention may be developed, and all such modifications are deemed to be within the scope of the present invention as defined by the appended claims.

* * *

CLAIMS

What is claimed is:

1. A method of producing an all glass, non-porous, multi-component photonic band-gap fiber comprising:

creating a preform having a plurality of low refractive index glass rods and a plurality of high refractive index optical glass rods arranged in a predetermined pattern between the low refractive index glass rods;

heating and drawing the preform to form a non-porous photonic band-gap fiber.

2. The method of claim 1 further comprising:

arranging the low-refractive index glass rods and the high refractive index glass rods in concentric rings in the preform, with a low refractive index glass rods being located in the center of the preform.

3. The method of claim 1 further comprising:

assembling a first stage preform subassembly having a predetermined number of the low refractive index glass rods and the high refractive index glass rods arranged in a predetermined pattern;

heating and drawing the first stage subassembly preform to form drawn first stage subassemblies; and

creating the preform from a plurality of the drawn first stage subassemblies.

4. The method of claim 1 further comprising:

assembling a plurality of the non-porous photonic band-gap fibers together to form a photonic band-gap array.

5. The method of claim 1 further comprising:

adding a third plurality of medium refractive index glass rods to the preform in a predetermined pattern between the first plurality of low refractive index glass rods and the second plurality of high refractive index glass rods.

6. The method of claim 1 further comprising:

adding a gain medium to the preform in a predetermined pattern between the first plurality of low refractive index glass rods and the second plurality of high refractive index glass rods.

7. A method of producing an all glass, non-porous, multi-component photonic band-gap multiple index array comprising:

creating a first photonic band-gap optical fiber by assembling a first preform having a plurality of low refractive index glass rods and a plurality of high refractive index glass rods arranged in a predetermined pattern between the low refractive index glass rods, and heating and drawing the first preform to form a first drawn non-porous subassembly having a first index;

creating a second photonic band-gap optical fiber by assembling a second preform having a plurality of low refractive index glass rods and a plurality of medium refractive index glass rods arranged in a predetermined pattern between the low refractive index glass rods, and heating and drawing the second preform to form a second drawn non-porous subassembly having a second index; and

assembling a third preform from the first and second drawn non-porous subassemblies, and heating and drawing the third preform to form a non-porous, multi-component photonic band-gap multiple index array.

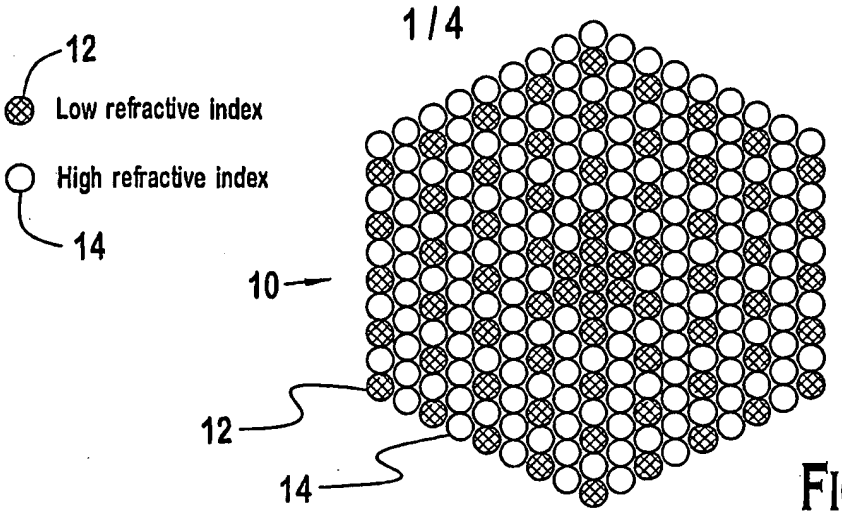


FIG. 1

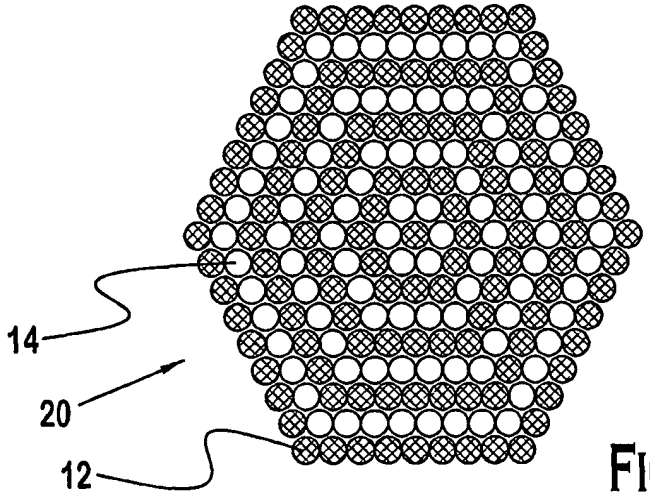


FIG. 2

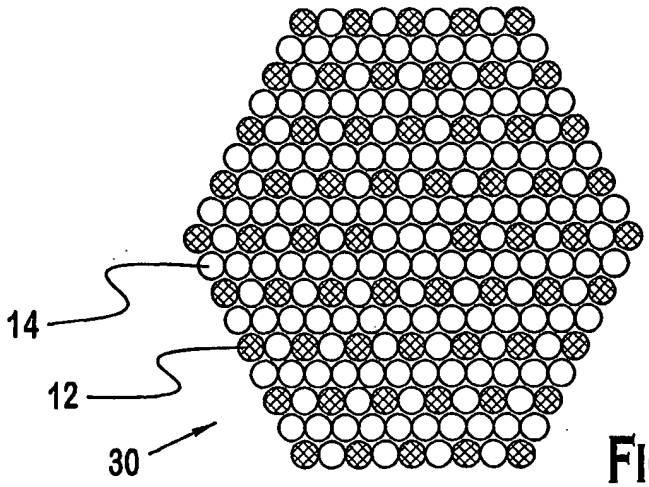


FIG. 3

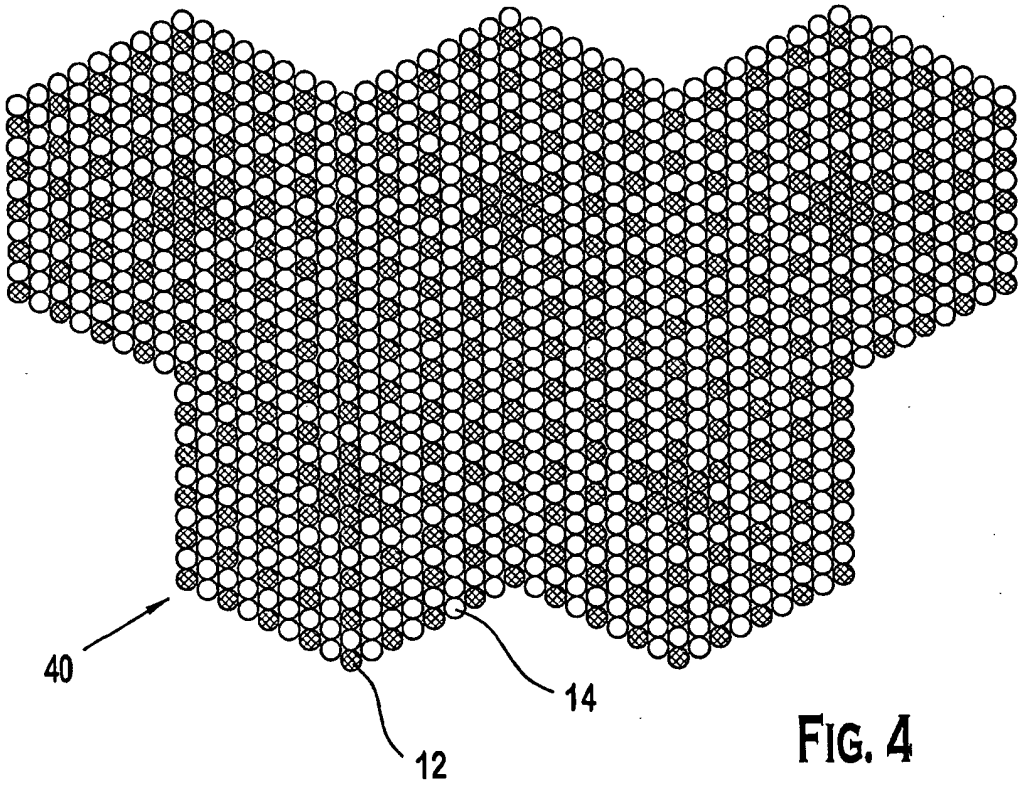


FIG. 4

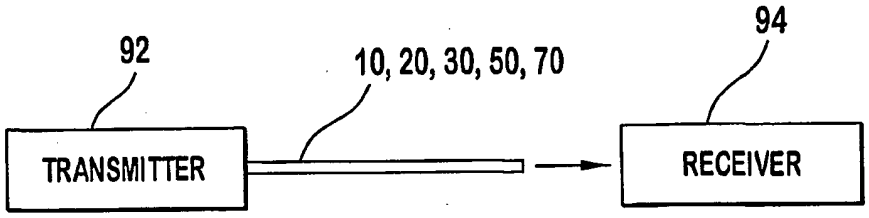


FIG. 10

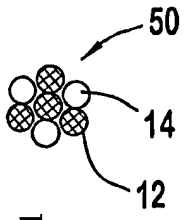


FIG. 5

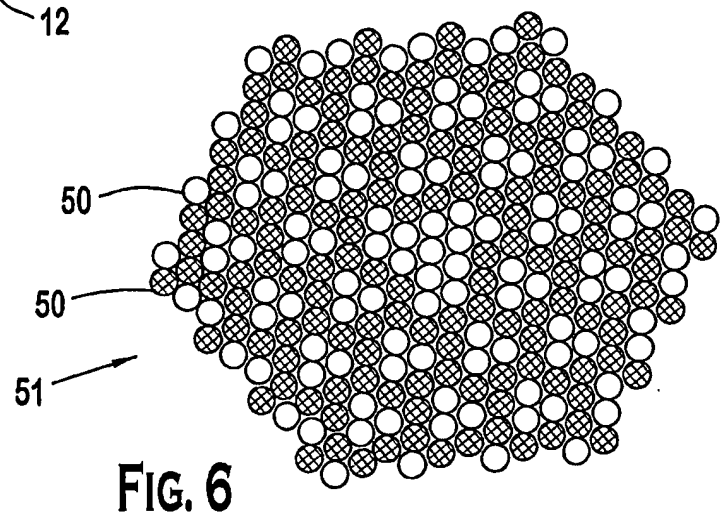


FIG. 6

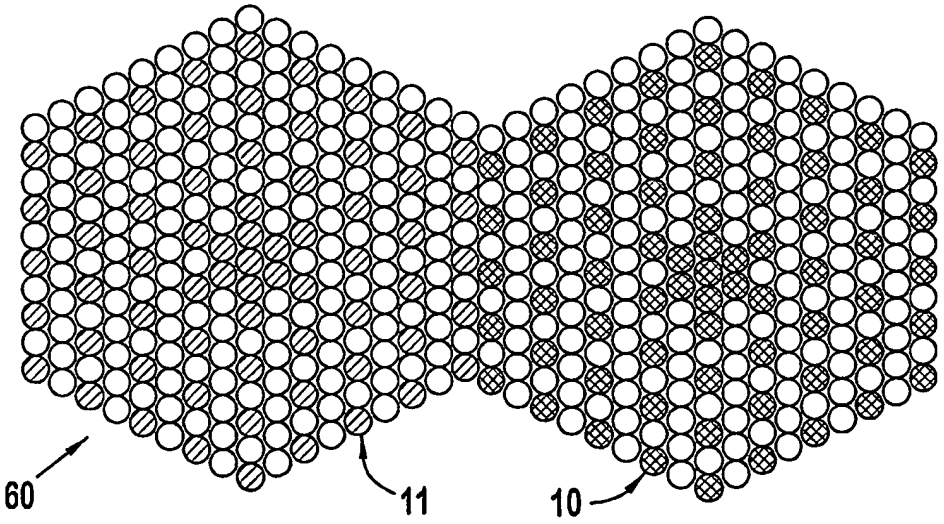
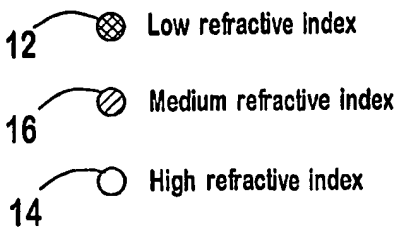


FIG. 7



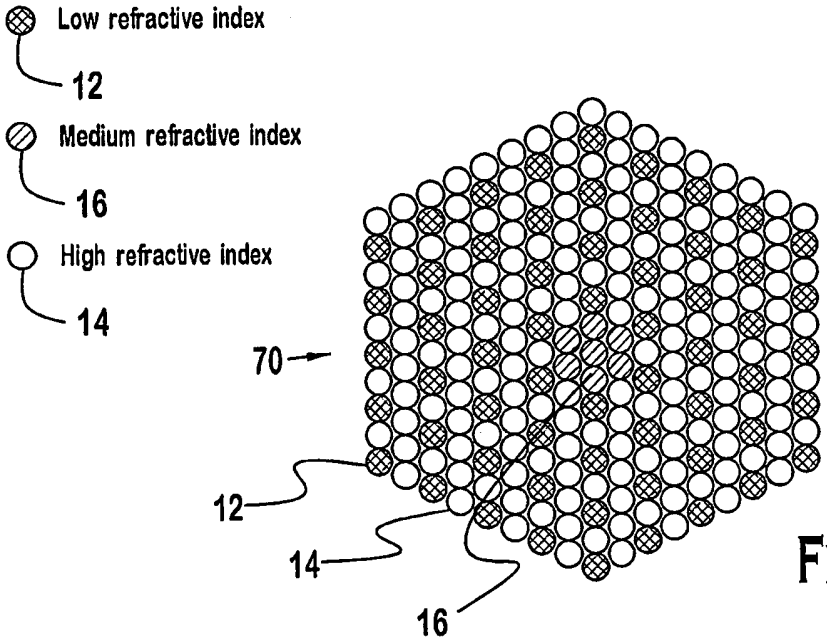

Low refractive index
12
Medium refractive index
16
High refractive index
14
70
12
14
16

FIG. 8

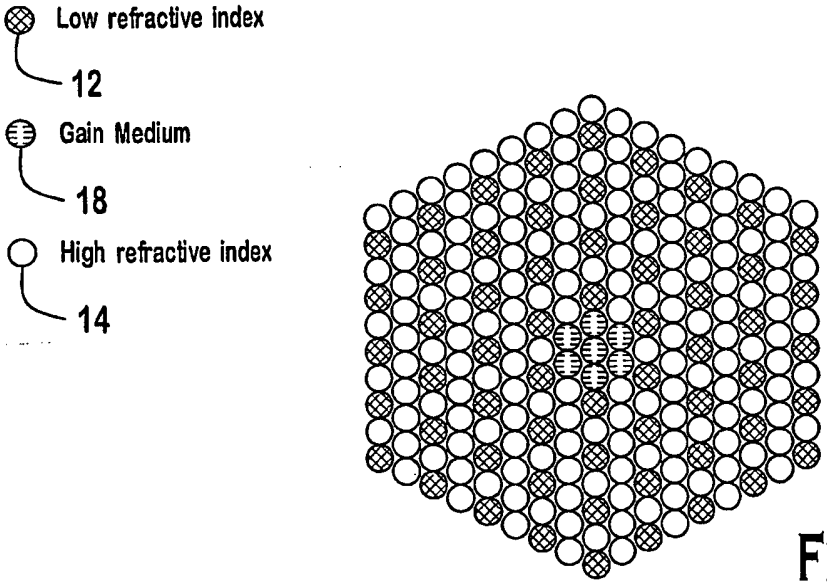

Low refractive index
12
Gain Medium
18
High refractive index
14

FIG. 9

INTERNATIONAL SEARCH REPORT

Ir tional application No.
PCT/US01/28379

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :C03B 37/028
US CL :65/409, 411

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 65/409, 411

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	US 6,301,420 B1 (GREENAWAY et al) 09 October 2001, figure 1, col. 3, line 58, col. 4, lines 13-15, 28-39.	1-2, 6
Y,P		4-5

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
17 NOVEMBER 2001	07 DEC 2001
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JOHN HOFFMANN Telephone No. (703) 308-0651

Form PCT/ISA/210 (second sheet) (July 1998)★